Beyond Hypothermia: Emerging Therapies for Neuroprotection

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

The clinical presentation and grading the severity of infants with HIE will be discussed. Evidence-based management will be reviewed, as well as new adjunct therapies for managing the infant with HIE.

Session Objectives

Upon completion of this presentation, the participant will:

- understand the clinical presentation of infants with HIE;
- understand the grades of severity of HIE;
- be able to cite the current literature on modest hypothermia in the management of HIE;
- be able to identify newer adjunct therapies for management of infants with HIE.

References

References for this session can be found throughout the speaker’s powerpoint presentation. A complete reference list can be obtained on request.

Session Outline

See presentation handout on the following pages.
Beyond Hypothermia: emerging therapies for neuroprotection

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Lecture Outline

• I. General
• II. Pathophysiology
• III. Clinical Presentation
• III. Current Treatments
  – Supportive
  – Hypothermia
• IV. Future Treatments
  – Glutamate Receptor Antagonist
  – Antioxidants
  – Anti-Apoptotic Factors
  – Stem Cell Therapy
• V. Summary

I. General

• Incidence of systemic asphyxia is 2 to 4 out of 1,000 full-term neonates.
• 20-50% of neonates with HIE die during the newborn period.
• Those who survive, 25% develop permanent neurologic handicap.

II. Pathophysiology

Axon

EAATs

Astrocyte

Glu

ADP

NH₃
+ ATP

Na⁺

Gln

Glu

KA

AMPA

NMDA

Ca²⁺

Glu

Gln

FANNP 25TH NATIONAL NNP SYMPOSIUM: CLINICAL UPDATE AND REVIEW

A7a: BEYOND HYPOTHERMIA: EMERGING THERAPIES FOR NEUROPROTECTION
II. Pathophysiology

EAATs

Astrocyte

\[ \text{Na}^+ \text{Lipases} \]

Acts on Cell membrane

Axon

Glu

Glu

Glu

\[ \text{KA} \]

AMPA

NMDA

\[ \text{Ca}^{++} \uparrow \]

NO Synthetase

Free Radical

Mg

Ca++

Degradation of microtubules

Nucleases


Risk factors for neonatal encephalopathy

Many neonates with neonatal encephalopathy do not have evidence of hypoxia/ischemia or asphyxia. Several risk factors have been identified:

Antepartum:
- Maternal hypotension
- Infertility treatment
- Thyroid disease

Intrapartum:
- Forceps delivery
- Breech presentation
- Placental abruption
- Prolapsed cord

Severity of HIE

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>MODERATE HIE</th>
<th>SEVERE HIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Level of consciousness</td>
<td>2 = Lethargic</td>
<td>3 = Stuporcoma</td>
</tr>
<tr>
<td>2. Spontaneous Activity</td>
<td>2 = Decreased activity</td>
<td>3 = No activity</td>
</tr>
<tr>
<td>3. Posture</td>
<td>2 = Distal flexion, complete extension</td>
<td>3 = Desperate</td>
</tr>
<tr>
<td>4. Tone</td>
<td>2a = Hypotonia (local or general)</td>
<td>3a = Flaccid</td>
</tr>
<tr>
<td>5. Primitive Reflexes</td>
<td>2 = Weak or has bite</td>
<td>3 = Absent</td>
</tr>
<tr>
<td>6. Autonomic System</td>
<td>2 = Bradycardia</td>
<td>3 = Variable</td>
</tr>
<tr>
<td>Heart rate</td>
<td>2 = Periodic breathing</td>
<td>3a = on vent with spontaneous respirations</td>
</tr>
<tr>
<td>Respiration</td>
<td>2 = Hyperpnea</td>
<td>3b = on vent without spontaneous breathing</td>
</tr>
</tbody>
</table>

Encephalopathy Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score 0</th>
<th>Score 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding</td>
<td>Normal</td>
<td>Geaghe, gastrostomy tube or tube, not tolerated and feeding</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Abdominal distension, distension, or diarrhea</td>
<td></td>
</tr>
<tr>
<td>Manometrics</td>
<td>Normal</td>
<td>Hypomotility or hypotonia</td>
</tr>
<tr>
<td>Respiratory status</td>
<td>Normal</td>
<td>Respiratory distress (short or sustained positive airway pressure or mechanical ventilation)</td>
</tr>
<tr>
<td>Rear</td>
<td>Normal</td>
<td>Hyperflexion, hypotonia, or oars</td>
</tr>
<tr>
<td>Seizure</td>
<td>None</td>
<td>Resistant or confirmed clinical seizures</td>
</tr>
</tbody>
</table>


Subsequent exams

Serial exams are a good clinical predictor and biomarker of outcome

Although infrequent, the presence of hypertonia, fisted hand, abnormal movements, absent gag, asymmetric tonic neck reflex, need for gavage/gastrostomy tube feedings at discharge increased risk of death and disability at 18 months
III. Current Therapies

- Hypothermia

### Benefits of Hypothermia

- **Reduction in glutamate release**
- **Decrease in intracellular acidosis and lactic acid accumulation**
- **Preservation of endogenous antioxidants**
- **Reduction of leukotriene production**
- **Prevention of blood-brain barrier disruption and brain edema**
- **Reduction in cerebral metabolism**
- **Inhibition of apoptosis**
III. Hypothermia - Future

- Late hypothermia at 6-24 hours after injury.
  - NICHD (16 centers) trial with a target enrollment of 168 neonates
  - This study is a randomized, placebo-controlled, clinical trial with neonates randomized to either receive hypothermia (96 hours) or participate in a non-cooled control group.
  - Start April 2008 with targeted completion March 2013 (slow enrollment)

Current Treatment Option:
Moderate Hypothermia (32-34°C)

>40% Cooled Babies have poor outcome

<table>
<thead>
<tr>
<th></th>
<th>Cooled</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died or severe disability</td>
<td>44-55%</td>
<td>62-66%</td>
</tr>
<tr>
<td>Died</td>
<td>24-33%</td>
<td>27-38%</td>
</tr>
<tr>
<td>Bayley MDI &lt; 70</td>
<td>25-30%</td>
<td>35-39%</td>
</tr>
<tr>
<td>Bayley PDI &lt; 70</td>
<td>24-30%</td>
<td>34-41%</td>
</tr>
</tbody>
</table>

IV. Future Therapies

Only 1 in 8 children will benefit from hypothermia

Ideal Neuroprotective Intervention

- Safe
- Readily available
- Inexpensive
- Developmentally appropriate
- Target mechanisms of injury
- Prevent injury, foster normal development (preterm)
  - and/or
- Effective treatment after injury (HIE, IVH)

IV. Future Treatments

- Glutamate Receptor Antagonist
IV. Glutamate Receptor Antagonist Magnesium

- Magnesium
  - Magnesium prevents neuronal death from excitatory amino acids.
  - Pretreatment may be protective; therapy during asphyxia or post injury +/- reduce cerebral injury in animal models.

- MagCool
  - Placebo controlled trial
  - dose of 250mg/kg IV q 24 hrly for 3 doses
  - 300 babies
  - Severe Neurodevelopmental Disability will be assessed at discharge from hospital and at 18-24 months of age to assess developmental delay and cerebral palsy using the Bayley Scale of Infant Development II
  - Egypt

- Multicenter trial
- 37 weeks or greater
- 5 minute Apgar score of 7 or less and either failure to initiate spontaneous respiration at 10 minutes after birth or occurrence of clinical seizures within 24 hours.
- Mg infusion within 24 hours of birth.
  - MgSO4 was give at a dose of 250mg/kg for 3 days.

IV. Glutamate Receptor Antagonist
Magnesium
- The primary outcome was the composite of stillbirth or infant death by 1 year of age or moderate or severe cerebral palsy, as assessed at or beyond 2 years of age (with ages corrected for prematurity).


IV. Glutamate Receptor Antagonist
Xenon
- Noble gas that rapidly reaches equilibrium with the brain when inhaled.
- Partial pressure in the brain will closely follow that delivered to the lungs.
- Effective anesthetic with a very rapid onset, no metabolism by the body, and no proven adverse hemodynamic side effects.
- Very expensive

Dingley, J.; Tooley, J.; Porter, H.; Thoresen, M., Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. Stroke 2006, 37, (2), 501-6

IV. Glutamate Receptor Antagonist
Xenon + Hypothermia
- Xenon is attractive as a combination therapy due to its lack of chemical reactivity, lack of clinical side effects, previous use in neonates, rapid reversibility, and lack of fetotoxicity.
- Approved for use as an anesthetic agent in Europe.


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IV. Glutamate Receptor Antagonist
Xenon + Hypothermia
- Single arm dose escalation trial.
  - Under 18 hours of age
  - Requiring less than 35% oxygen
  - Escalation from 3 to 18 hours of Xenon
  - Xenon dose of 25% (1 patient) and 50% (14 patients)

Xenon Ventilation During Therapeutic Hypothermia in Neonatal Encephalopathy: A Feasibility Study. Dingley et al. Pediatric 2014
IV. Glutamate Receptor Antagonist
Xenon + Hypothermia

• Breathing 50% Xenon for up to 18 hours in conjunction with 72-hour cooling in term and near term infants with HIE was feasible with no adverse effects.
  – No significant cardiovascular or respiratory changes.
  – Cuffed ETT did not affect extubation.
  – Xenon depressed EEG.

• Xenon depressed seizure activity.

• Outcome at 18 months showed no delay or mild delay in 50% of these patients.
  – Similar to and no worse than expected from cooling alone.

• Safe to proceed with Phase II trial
  – Study currently underway.

IV. Future Treatments - Erythropoietin

• Produced by
  – Fetal liver
  – Postnatal kidney

• Regulates hematopoiesis
  – Blocks apoptosis of erythrocyte precursors

• Essential for survival
IV. Future Treatments- Erythropoietin

- **Neurotrophic effects** (Campana et al., 1998, Ferriero et al 2009)
- Decreased glutamate toxicity (Morishita 1997; Kawakami 2001)
- Decreased apoptosis (Ivud 1998; Siren 2001; Celik 2002; Renzi 2002; Villa 2003)
- Decreased NO-mediated injury (Ozgur 2001; Kumral 2004)
- Antioxidant effects (Chattopadhyay 2000; Genc 2002)
- Protective effects on glia (Nagai 2001; Sugawa 2002; Yairanc 2002)
- Enhanced oligodendrogenesis (Iwai 2010, Zhang 2010)
- Enhanced regulation of breathing (Khenni 2012)

### Effects on Repair

- Angiogenesis
- Neurogenesis

IV. Future Treatments- Erythropoietin

- Risks (adults with chronic renal failure)
  - Hypertension
  - Clotting
  - Polycythemia
  - Seizures
  - Rash
  - Death

These risks have never been reported in infants

- The risk of ROP and hemangiomas must be assessed in preterm infants

IV. Future Treatments

**EPO- HIE**

- Two clinical trials:
  - Neurological outcome after erythropoietin treatment for neonatal encephalopathy.
    - Performed in Austria/China
    - Performed between August 2003 and January 2007.
    - Neonates 37 weeks and greater.
    - Epo given within 48 hours of birth
      - First dose given subcutaneously then IV every other day for 2 weeks.

## IV. Future Treatments - EPO- HIE

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods:</strong></td>
<td>Erythropoietin dose-escalation open-label study, N=24</td>
<td>All subjects met criteria for moderate HIE and were cooled</td>
<td>Infants received up to 6 doses of Epo IV QOD starting at &lt;24h of age</td>
</tr>
<tr>
<td></td>
<td>250 (N=3), 500 (N=6), 1000 (N=7), 2500 U/kg/dose (N=8)</td>
<td>There were no safety issues identified</td>
<td>There were no safety issues identified</td>
</tr>
</tbody>
</table>

### EPO- HIE

**NEAT 1 Follow Up**
- 24 infants were followed for 22 +/- 7.4 months.
- There were no deaths (6 expected)
- 1 child (4.5%) had a moderate to severe disability; this child had quadriplegic CP and GMFCS 3 (6 expected)
- MRI findings:
  - 11 (50%) had a normal brain MRI had a normal outcome
  - 8 (36%) had moderate to severe brain injury on MRI, including the patient with moderate to severe disability
  - 7 had moderate to severe watershed distribution injury exhibited the following outcomes: normal (3), mild language delay (2), mild hemiplegic CP (1) and epilepsy (1)

### EPO- HIE

**Ongoing studies of Epo for HIE in term infants:**
- H Liley, Australia: PAEAN study (phase III funded)
  - N= 300, Epo 1000 U/kg; protocol matches ours
- J Patkai, France (phase III, enrolling)
  - N = 330, Epo 1000U/kg + HT
- M Baserga, US (phase I completed)
  - Darbepoietin + HT
- A Pappas/S Shankaran: NICHD NRN
  - Phase II/III Epo + HT (proposed study– details unclear)

### EPO- HIE

**Phase I Trial of Neonatal Epo in Perinatal HIE (NEAT Trial)**

- All subjects met criteria for moderate HIE and were cooled
- 250 (N=3), 500 (N=6), 1000 (N=7), 2500 U/kg/dose (N=8)
- Infants received up to 6 doses of Epo IV QOD starting at <24h of age
- There were no safety issues identified

**DANCE Trial** (Darbepoetin administration in newborns undergoing cooling for encephalopathy. Safety and pharmacokinetics)
- 30 subjects
  - Placebo
  - 2 microgram/kg x 2
  - 10 microgram/kg x 2
- Results: No safety issues, pharmacokinetic profiles developed

### IV. Antioxidants

**Allopurinol**
- Allopurinol scavenges free radicals such as hydroxyl, chelates free iron, and inhibits lipid peroxidation.
- Animal models have found that the xanthine oxidase inhibitor allopurinol limit the degree of post-asphyxia brain injury.
- Most common reported side is a skin rash and hypersensitivity reaction.

**References:**
IV. Antioxidants

Allopurinol

- 3 human trials which enrolled 114 patients (Benders 2006, Gunes 2007, and van Bel 1998).
- Term or near-term infants with HIE.
- Allopurinol was administered in total daily doses of 40 mg/kg within 4 hours of birth.
- Continued for 1 day (Benders and van Bel) or 3 days (Gunes).


IV. Antioxidants

Allopurinol - Hypoplastic Left Heart Syndrome

- During a period of planned hypothermia and circulatory arrest, allopurinol pre-treatment reduced a composite outcome of
  - death
  - adverse neurological
  - or cardiac outcomes


V. Future Therapies - Additional agents

- Allopurinol
- Polyphenols found in Pomegranate juice/Resveratol
- Melatonin
- Topirimate/levetiracetam (Keppra)
- NAC
- cannabinoids

V. Summary

Neonate >36 weeks with history consistent with HIE

Resuscitation:
- RA versus 100% oxygen mixture
- Hypothermia or temperature control in the DR
Neonate >36 weeks with a diagnosis of HIE

Systemic supportive Care

Stratify Neonate

PE

aEEG

Cerebral mixed saturations

Biomarker

Supportive Care

Mild

Moderate

Severe

0-24 hours

Hypothesis

Pharmacologic Agents

Re-Stratify Neonate

PE

aEEG

Cerebral mixed saturations

Biomarker

MRI with DWI

Moderate

Continue Hypothermia

For 72 hours

Severe

Continue pharmacologic intervention

Stem Cell Therapy at 7-10 days?